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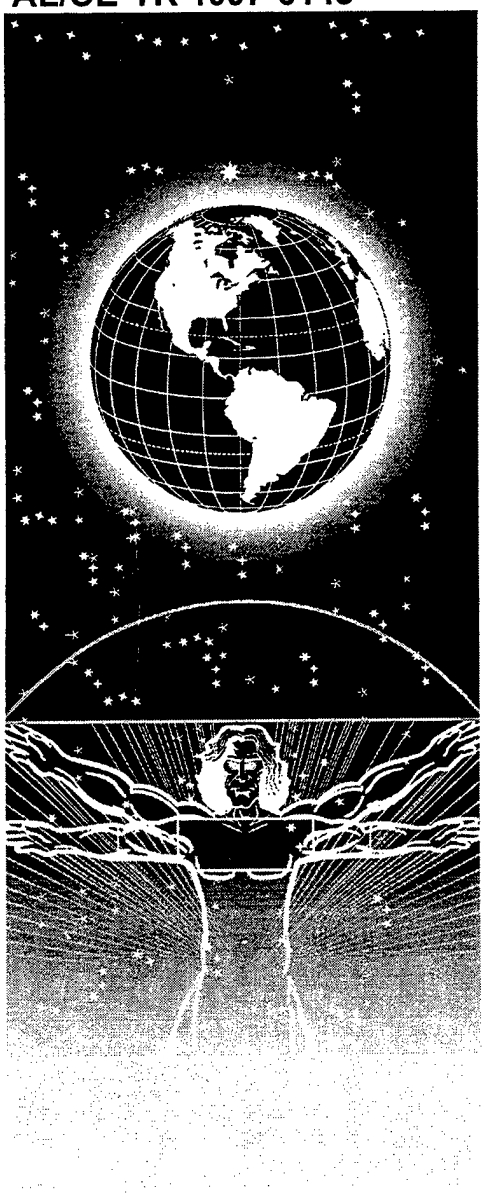

UNITED STATES AIR FORCE
RESEARCH LABORATORY

ACUTE INHALATION TOXICITY EVALUATION OF A 93:7 MIXTURE OF PERFLUORO-2-BUTENE AND 1-BROMOPROPANE, A REPLACEMENT CANDIDATE FOR OZONE DEPLETING SUBSTANCES

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October 1997

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TECHNICAL REVIEW AND APPROVAL

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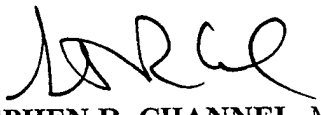
The animal use described in this study was conducted in accordance with the principles stated in the "Guide for the Care and Use of Laboratory Animals", National Research Council, 1996, and the Animal Welfare Act of 1966, as amended.

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

FOR THE DIRECTOR



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The DoD requires the development of toxicity profiles for chemical substitute candidates proposed to replace ozone depleting substances such as chloro- and fluorocarbons and halons. A 93:7 mixture of perfluoro-2-butene and 1-bromopropane was identified as a possible replacement candidate for ozone-depleting fire extinguishants An acute inhalation toxicity test utilizing male and female Fischer 344 rats was performed on this test material. No deaths occurred in any of the rats exposed to 5.3 mg/L of the 93:7 perfluoro-2-butene and 1-bromopropane mixture. Body weights of male and female rats during the subsequent 14-day observation period were unaffected by treatment. The test material did not produce acute toxicity via the inhalation route.

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PREFACE

This is one of a series of technical reports describing results of the experimental laboratory programs conducted at the Toxicology Division under the ManTech/Geo-Centers Joint Venture Toxic Hazards Research Contract. This document serves as a final report on the acute inhalation toxicity of the 93:7 mixture of perfluoro-2-butene and 1-bromopropane, a replacement candidate for ozone depleting substances. The research described in this report began in July 1997 and was completed in August 1997 under Department of the Air Force Contract No. F41624-96-C-9010. Lt Col Terry A. Childress served as the Contracting Officer's Representative for the U.S. Air Force, Armstrong Laboratory. Darol E. Dodd, Ph.D., served as Program Manager for ManTech/Geo-Centers Joint Venture.

The animals used in this study were handled in accordance with the principles stated in the *Guide for the Care and Use of Laboratory Animals*, Institute of Laboratory Animal Resources, National Research Council, National Academy Press, 1996, and the Animal Welfare Act of 1966, as amended. The authors gratefully acknowledge the technical assistance of Richard J. Godfrey, Jerry W. Nicholson, Margaret A. Parish, and Darol E. Dodd, Ph.D.

ABBREVIATIONS

amu	Atomic mass unit
°C	Degrees Centigrade
CFCs	Chlorofluorocarbons
DoD	Department of Defense
F-344	Fischer 344 rat(s)
g	Gram
GC	Gas chromatograph
h	Hour(s)
I.D.	Inner diameter
L	Liter
LC_{50}	Lethal concentration for 50% of exposed animals
M	Meter
mg	Milligram
mL	Milliliter
mm	Millimeter
mmHg	Millimeter of mercury
SD	Standard deviation
µm	Microns

SECTION I

INTRODUCTION

Fire extinguishant agents, refrigerants, and other solvents presently in the Department of Defense (DoD) and worldwide inventory contain halogenated fluorocarbons. Chloro- and bromofluorocarbons (halons) are substances thought to cause ozone depletion in the stratosphere. Environmental concern over this ozone depletion by activity of chlorine radicals from chlorofluorocarbons (CFCs) has led to an international treaty called the Montreal Protocol (1987) which calls for the phaseout of select CFCs and halons by the year 2000. The potential utility of a number of chemical substitutes that have little or no ozone depleting potential are being investigated to meet the demand for alternatives to CFCs and halons.

The DoD requires the development of a toxicity profile for the potential chemical replacements, which includes the results of acute toxicity testing. Because these replacements are currently being developed and are not manufactured commercially, very little, if any, toxicity information is available in the literature. To initiate responsible industrial hygiene practice within the production area and provide or recommend appropriate protective equipment in the workplace, it is necessary that the operations personnel are aware of the acute health hazards of this compound.

A 93:7 mixture of perfluoro-2-butene and 1-bromopropane is one of the chemical replacement candidates being considered for ozone depleting substances. Perfluoro-2-butene is a nonflammable gas and considered mildly toxic by inhalation based on mutation data reports (Lewis, 1991). According to a Material Safety Data Sheet distributed by Aldrich Chemical Company, Inc., Milwaukee, WI (07/17/96), 1-bromopropane vapor is irritating to the eyes, mucus membranes, and upper respiratory tract. The 30-minute LC_{50} value in rats is 253 mg/L. 1-Bromopropane is a highly flammable colorless liquid (IOSHIC, 1989) and irritates the skin. Long-term exposure to 1-Bromopropane can cause hepatic and renal damage (IOSHIC, 1989).

The toxicity associated with acute exposure to the 93:7 mixture of perfluoro-2-butene and 1-brompropane is not known; therefore, an acute inhalation limit test was performed to determine the toxicity associated with acute inhalation exposure to the mixture. The data obtained from this inhalation toxicity test will provide a measure of toxic potency that can be compared with other chemicals, including other CFCs and halon replacement candidates. The species and sex of animals selected for this acute toxicity test were in conformance with the requirements of the U.S. Environmental Protection Agency (1982). Existing alternative methods to animal testing were inadequate for use in this study.

SECTION II

MATERIALS AND METHODS

Test Material

Approximately 300 mL of the 93:7 mixture of perfluoro-2-butene and 1-bromopropane was provided by Mr. Barry Mitchell, WL/FIVCTF, Tyndall AFB, FL. Pertinent chemical and physical properties of the individual components of the test material mixture are listed below.

Perfluoro-2-butene

Source:	Synquest Laboratories, Inc., Alachua, FL
CAS No.:	360-89-4
Boiling Pt.:	1.2 °C
Molecular Weight:	200.04
Vapor Density: (Air = 1)	7
Specific Gravity:	1.5 g/mL
Appearance:	Nonflammable gas

1-Bromopropane

Source:	ACROS Organics, Geel, Belgium
CAS No.:	106-94-5
Boiling Point:	71 °C
Molecular Weight:	122.99
Vapor pressure:	146 mmHg @ 20 °C
Specific Gravity:	1.354 g/mL
Appearance:	Colorless liquid

A sample of the test material used in this study was analyzed for its composition. Dilutions in room air, down to ~ 0.3% of the total test material, were prepared for the analysis which uses combined gas chromatography - mass spectometry and the headspace sample introduction technique.

The analyses yielded five major components:

both isomers of C_4F_8	~ 72.2%
1,1,1,3,3,3-hexafluoropropane	~ 2.45%
unknown fluorocarbon	~ 13.2 %
C3H7Br	~ 12.1%

The samples were analyzed twice. The second time included ions below 47 amu in order to produce a more representative area for the 1-bromopropane, since its main ion is 43 amu. There were also traces (<0.1%) of CF_3I and at least one other compound which was so weak in intensity it produced only a single -CF_3 fragment.

Test Animals

Fischer 344 (F-344) rats (CDF®[F-344]CrlBR), 7 weeks of age, were purchased from Charles River Breeding Laboratory, Wilmington, MA. All animals were identified by tattoo and subjected to a two-week acclimation period. Rats were group housed (two per cage, separated by sex) in clear plastic cages with wood-chip bedding (Sani-Chip®, P.J. Murphy Forest Products, Montville, NJ). Water and feed (Certified Rodent Diet #5002, PMI Feeds, Inc., St Louis, MO) were available *ad libitum*, except for 12 h prior to oral dosing. Animal room temperatures were maintained at 21 to 25 °C and the light/dark cycle was set at 12-h intervals.

Experimental Design

Acute Inhalation Toxicity Limit Test

Five male and five female F-344 rats were exposed for 4 h to a target concentration of 5 mg/L of the perfluoro-2-butene/1-bromopropane mixture. Exposures were performed using a nose-only inhalation chamber (Cannon et al., 1983). Animal body weights were recorded prior to exposure and 1, 2, 4, 7, and 14 days post-dosing. Animals were observed twice daily during the postexposure period, and clinical signs of toxic stress were recorded. Rats were

euthanatized (CO_2 inhalation) and gross pathology performed on Day 14 postexposure. No further testing of this mixture was performed since no compound-related mortality was observed at the limit test concentration of 5 mg/L.

Exposure Atmosphere Generation and Analysis

At normal room temperature and pressure, the liquid test material vaporized completely. A five-liter Tedlar sample bag was used to contain the amount needed for the animal exposure. The test material was pressurized for introduction into a flowing air line by compression and delivered through a flow control valve and flow meter, countercurrent to the direction of the chamber inlet air flow. The air supply for the animal exposure was initially chosen at five liters per minute, but the control of test material input improved at higher flow rates. Thus, after a few minutes of operation, the chamber air flow was increased to 10 liters per minute and then finely controlled as required by results of chamber atmosphere analysis of the test material.

The average molecular weight (194.6) was determined on the basis of the reported concentration mix (93:7) as received. Standards were prepared by quantitative dilution of the concentrate with air in Tedlar bags bracketing the range of the limit test. A Varian 3400 gas chromatograph (GC) equipped with a 15-M x 0.53 mm SPB-5 fused silica column, loop injector (Supleco, Bellefonte, PA: Model 2-5304, Lot #1133120, I.D. 0.53 μm), flame ionization detector and an inboard integrator was used for the analysis of both the standards and the exposure atmosphere. Three injections every five minutes were made for each data point. The total peak area of the 6 peaks was used for plotting both the calibration data and calculating concentrations. Appendix A contains calibration data for the GC analyses of perfluoro-2-butene and 1-bromopropane.

SECTION III

RESULTS

Five male and five female rats were exposed to the test material/air atmosphere for four hours. The mean concentration for the exposure was 5.3 mg/L (SD 1.2). Appendix B contains representative sampling runs during the animal exposure.

No deaths resulted from the acute inhalation exposure and no signs of toxicity were observed either during exposure or postexposure. All male rats and four of five female rats gained weight over the 14-day observation period (Table 1). One female lost weight during the postexposure observation period. No gross lesions were observed at necropsy for any animal on study.

TABLE 1. BODY WEIGHTS[a] OF MALE and FEMALE RATS AFTER ACUTE INHALATION EXPOSURE TO PERFLUORO-2-BUTENE AND 1-BROMOPROPANE

	Study Day				
Animal Number	**0**	**1**	**2**	**7**	**14**
Male					
01	236.6	231.2	234.2	245.3	259.5
02	243.5	236.1	237.2	251.8	268.9
03	227.5	221.7	224.1	238.6	257.0
04	239.2	235.7	235.6	251.6	272.4
05	227.3	225.4	224.2	237.6	253.5
Mean	**234.8**	**230.0**	**231.1**	**245.0**	**262.3**
SD	**7.2**	**6.3**	**6.4**	**6.8**	**8.0**
Female					
06	134.5	130.3	133.1	136.6	142.6
07	127.5	133.9	134.0	136.5	143.2
08	156.8	153.3	155.8	157.5	167.5
09	148.1	145.6	142.7	148.1	147.2
10	144.2	143.3	143.6	148.1	151.0
Mean	**142.2**	**141.3**	**141.8**	**145.4**	**150.3**
SD	**11.5**	**9.2**	**9.2**	**8.9**	**10.2**

[a]Weight in grams.

SECTION IV

DISCUSSION

In this acute inhalation toxicity study using a 93:7 mixture of perfluoro-2-butene and 1- bromopropane, no deaths or signs of toxic stress were observed in any of the animals exposed at the limit test value of 5 mg/L. A mild decrease in body weight following exposure is common in inhalation exposure systems requiring animal restraint and is considered a consequence of animal stress. Under the conditions of the limit test performed in this laboratory, the test material did not demonstrate an acute toxicological hazard when administered by the inhalation route.

SECTION V

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APPENDIX A

GC CALIBRATION FOR PERFLUORO-2-BUTENE / 1-BROMOPROPANE MIXTURE

Concentration (mg/L)	Peak 1 Area	% of Total Peak 1 Area	Peak 2 Area	% of Total Peak 2 area	Total Area
2.5	76881	90.8	7764	9.2	84645
2.5	75635	91.4	7153	8.6	82788
5	156135	91.0	15518	9.0	171653
5	153317	90.5	16073	9.5	169390
5	159468	90.9	15908	9.1	175376
7.5	254419	91.0	25114	9.0	279533
7.5	242178	90.4	25824	9.6	268002
	Mean %	**90.9**		**9.1**	

APPENDIX B

ANIMAL EXPOSURE DATA

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REPRESENTATIVE ANALYTICAL RUNS DURING THE EXPOSURE

Run #	Peak 1	Peak 2	Sum	Total Area	Concentration (mg/L)	% Peak 1	% Peak 2
90	52979	5359	58338			90.8	9.2
	52506	5302	57808			90.8	9.2
	44699	4517	49216	165362	4.8	90.8	9.2
100	53872	5457	59329			90.8	9.2
	53779	5442	59221			90.8	9.2
	53287	5411	58698	177248	5.5	90.8	9.2
110	53534	5365	58899			90.9	9.1
	53573	5399	58972			90.8	9.2
	53135	5390	58525	176396	5.1	90.8	9.2
120	52042	5241	57283			90.9	9.1
	51520	5192	56712			90.8	9.2
	51572	5162	56734	170729	5.0	90.9	9.1
Mean						**90.8**	**9.2**